IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Julie Straub, Howard Bernstein, Donald E. Chickering, III, Sarwat Khattak, and Greg Randall

Serial No.: 09/706,045 Art Unit: 1617

Filed: November 3, 2000 Examiner: E. Webman

For: *POROUS DRUG MATRICES AND METHODS OF MANUFACTURE THEREOF*

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.131

Sir:

We, Julie Straub and Howard Bernstein, hereby declare that:

1. We are co-inventors of the above-identified application.

2. We conceived of and reduced to practice a method of forming microparticles that contain a diagnostic agent, which was subsequently described in U.S. Patent No. 6,565,885 to Tarara et al. This method involves spray drying a feed stock containing the diagnostic agent, a surfactant and a blowing agent. We conceived of and reduced to practice this method prior to September 29, 1997, as demonstrated by the attached copies of pages from a laboratory notebook (Exhibit A).

3. As noted in Exhibit A, the feed stock to the spray drying apparatus contained ammonium acetate, lecithin, (poly(ethylene glycol)-co-poly(lactide-co-glycolide) (75:25), D,L-

poly(lactide), and air. This composition was emulsified using a VirTis homogenizer to form an emulsion, which was then spray dried using a small-scale lab spray dryer (see Exhibit A, page 14). The resulting microparticles had diameters ranging from 1-20 microns and were hollow with internal central-like voids containing the air bubble, as demonstrated by transmission electron microscopy (see Exhibit A, page 116). These microparticles were echogenic (see Exhibit A, page 105, injection 7).

4. I declare that all statements made herein of my own knowledge and belief are true and that all statements made on information and belief are believed to be true, and further, that the statements are made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 1-22-04

Julie Straub

Date: 1-22-04

Howard Bernstein

1517614_v1

EXHIBIT A

14 **TITLE** [illegible] 13 [illegible] 8/29/95

PROJECT NO.

BOOK NO. [redacted]

Investigator(s): H.Brush [illegible]
Notebook/page #:
Date: [redacted]
Microsphere lot #: [illegible]

Microsphere Production

Process Room Conditions

Room Temp.:	22°C
Room Humidity:	51.5% [illegible]

Polymer Preparation

Polymer type 1:	PLG-[illegible]
Source & Lot no.:	BPI [illegible]
Mass (g):	[illegible]
Polymer type 2:	D,L-PLA
Source & Lot no.:	[illegible]
Mass (g):	[illegible]
Solvent Type:	MeCl₂
Source & Lot no.:	EM, lot no [illegible]
Volume:	[illegible]
Surfactant type:	Lecithin
Surf. (Mat)/Vol.:	[illegible] mg
Dissolution Method:	Stirring
Dissolution Temp.:	Room temperature
Dissolution Time:	[illegible]
Excipient 1:	H_2O
Source & Lot no.:	House DI
Amount, g/ml:	[illegible]

Comments:
[illegible] ammonium acetate in water as follows:
[illegible] g in [illegible] of H_2O. Add [illegible] to polymer solution.

Spray Conditions

Cleaning Proc.:	[illegible]
Nozzle type:	[illegible]
Gas Pressure:	[illegible]
Gas Flow rate:	600 L/h
Gas type:	N₂ medical grade
Feed Flowrate:	112 [illegible]
Inlet Temp.:	50°C
Start Time:	1:16
Finish Time:	1:18
Mass Record:	[illegible] = 1.47
Yield (%):	27%

Process Conditions:

	Start 1:17	Middle 1:27	Finish
Outlet Temp.:	29°C	31°C	29°C
Filter vacuum:	-40 mbar	-[illegible]	-[illegible]

Comments:
Did not [illegible] inlet tube as I had done of a previous batches

Aeration Methodology

Sonication:	None
Horn type:	
Frequency:	
Power:	
Temperature:	
Time:	
Time until spray:	
Sparging:	None
Gas type:	
Gas pressure:	
Temperature:	
Time:	
Time until spray:	
Homogenization:	VIRTIS
Blade type:	macro ultra-fine generator
Time:	[illegible]
Speed:	[illegible] rpm
Temperature:	Ice bath
Time until spray:	~[illegible] minutes

Comments:

Drying Methodology

Type:	[illegible]
Total dry time:	[illegible]
Mass recovered:	[illegible]
Yield (%):	[illegible] 25%

Comments:
[illegible]

Sizing Methodology

Room Temp.:	
Room Humidity:	
Screening Time:	
Screen sizes:	
Screen type:	
Product recovered:	
Yield (%):	

Comments:

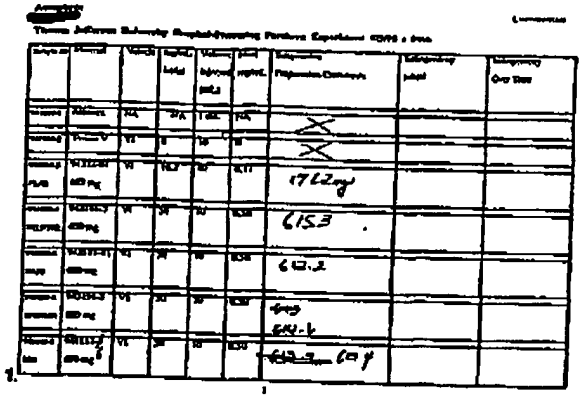
[illegible] [redacted]

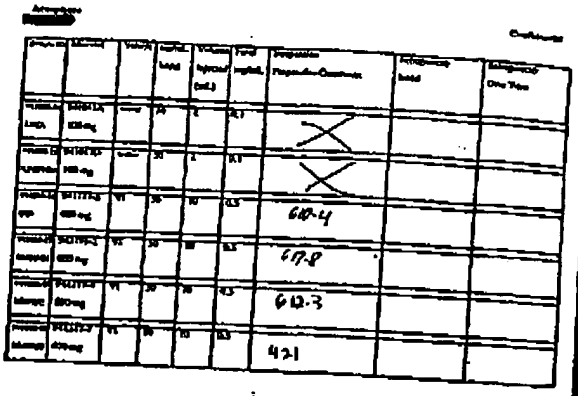
Work continued to Page 15

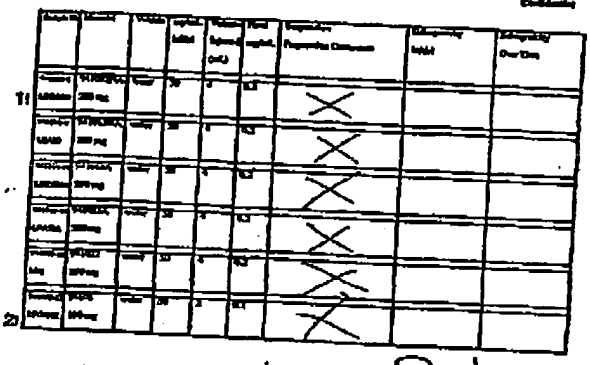
SIGNATURE [illegible] DATE [redacted]

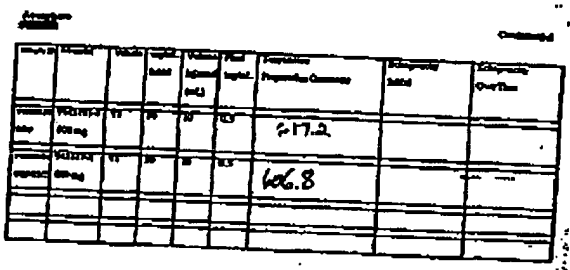
DISCLOSED TO AND UNDERSTOOD BY [illegible] [redacted] WITNESS DATE [illegible]

80 TITLE TJU Study For [redacted] PROJECT NO









Samples weighed by Howard in Dry Box on [redacted]. All but the 94108 2 and 94108 3 samples sent to Fogelberg on [redacted] by Airborne on dry ice / gel pak

SIGNATURE

DISCLOSED TO AND UNDERSTOOD BY

DATE [redacted] WITNESS

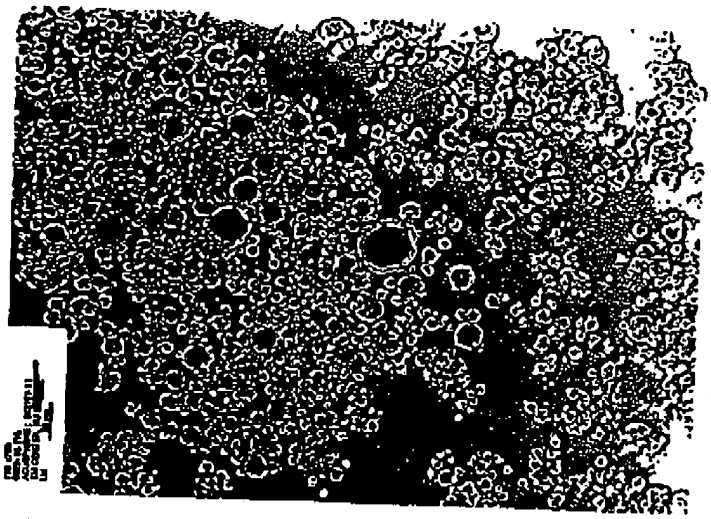
Work continued to Page 8 | 05

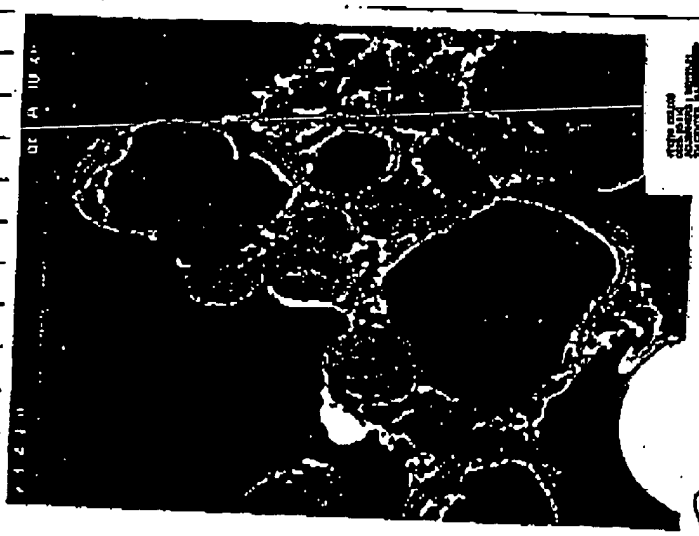
DATE [redacted]

DATE [redacted]

116

115





Work continued to Page

SIGNATURE

DISCLOSED TO AND UNDERSTOOD BY

DATE

WITNESS

DATE

106 TITLE PROJECT NO

[redacted]

Notes

All samples will be prepared by vortexing and sonication.

All samples will be precipitated in 20 mL scintillation vials. Empty 20 mL scintillation vials will be brought.

Saline (0.9%) will be used instead of water for the bath diluent in the pumping system. Precipitated samples of 163 g of $CaCl_2$ will be brought out, and diluted to 1800 mL with water in a bottle. Two such bottles will be sent to TRA. A total of 20 H_2O flasks will be brought.

Vehicle 1 = 0.9% Tween 20, 3% glycerol ← reversed

Vehicle 2 = 0.9% F127, 3.4% triethyl citrate/ethyl

1) System essentially same as [redacted] as previously, except 500mL saline in bottle
2) Vehicle 2 (VF) was used
3) Syringe was dried thoroughly
4) After injection of sample, sample was sheared, flow rate was then increased to 500-800mL/min until echogenic material detected by the oscilloscope, flow rate then dropped to 100-200 mL/min.
5) The "later vortex" moved dramatically with each pulse
6) Tubing was manipulated to remove bubbles. At least once (prior to injection 9) the assembly in charge of alignment. At that one detected error, the machine was realigned.
7) Cleaning procedures: (1) Water pumped to remove all material; then saline pumped in (2) Water emptied, saline added + pumped through.

(2) System pumped dry, saline pumped in

Work continued to Page

SIGNATURE		DATE [redacted]
DISCLOSED TO AND UNDERSTOOD BY	DATE [redacted] WITNESS	DATE

TITLE

Work [illegible]

8/84 | 105

Acusphere [redacted]

Confidential

94100-37

Injection #	Sample ID/Material (Vehicle, etc.)	Suspension Preparation	Echogenicity Initial	Echogenicity Over Time	[illegible]
1	Albunex 0.6	NA ([illegible])	none – [illegible] during [illegible]		NO
2	Albunex 0.5	NA ([illegible])	[illegible]		NO
3	Albunex 0.7	"	echogenic		[illegible]
4	Albunex (F)	V/83/V [illegible]	not echogenic		NO
5	3-VF-12ml	V/S2/V [illegible]	a little echogenic	too little to follow	yes
6	4-VF-12ml	V/S1/V/S1/V [illegible]	a little echogenic [illegible]	decrease over 1 min	yes
7	5-VF-12ml	V/S1/V [illegible]	echogenic ([illegible])	~ [illegible] min	[illegible]
8	94050-9 ([illegible]) Sh	4ml	echogenic [illegible]	< 1 min	yes
9	94050-11 ([illegible]) Sh	4ml	[illegible]	< 1 min	NO
10	Albunex 0.7ml	NA ([illegible])	slightly echogenic [illegible]	[illegible]	yes
11	94050-3 ([illegible])	V/S1/V/S1 [illegible]	[illegible] – bubbles in [illegible]	not long	[illegible]
12	18-VF-12	V/S1/V [illegible]	slightly echogenic	1-2 min	yes
13	19-VF-12	V/S1/V/S1/V [illegible]	none		yes
14	13-2ml H2O	Sh	8ml	[illegible]	1-2 min	yes
15	15-2ml H2O	Sh	2ml	echogenic [illegible]	1-2 min	yes
16	8 ([illegible]) Sh	4ml	echogenic [illegible]	1-2 min	yes

Acusphere [redacted]

Confidential

Injection #	Sample ID/Material	Suspension Preparation	Echogenicity Initial	Echogenicity Over Time	
	.55				
17	5 ([illegible])	[illegible] 1ml V/S1/V/S1/V	slightly echogenic [illegible]	gone 1-2 min	yes
18	6-VF-12	a few [illegible] V/S1/V/S1/V	none		[illegible]
19	8-VF-12	a few flakes V/S1/V/S1/V	none		NO
20	16-VF-12	a few flakes V/S1/V/S1/V	slightly echogenic [illegible]	< 1 min	yes
21	10 [illegible]	Sh 4ml	very very slight	< 1 min	NO
22	7 [illegible]	Sh 4ml	very very slight	< 30s	[illegible]
23	31-VF-12	V/S1/V/S1/V 10ml	very very slight	< 30s	[illegible]
24	14 [illegible] H2O	Sh 2ml	none		NO
25	17-VF-12	V/S2/V 10ml	none		NO
26	Albunex 0.7	NA	a little echogenic		
27					
28					
29					
30					
31					
32					

Study Read by TW on [redacted]

SCIENTIFIC BINDERY PRODUCTIONS CHICAGO [illegible] Made in USA

Work continued to Page ____

SIGNATURE [signature] DATE [redacted]

DISCLOSED TO AND UNDERSTOOD BY [signature] DATE [redacted] WITNESS DATE